Longitudinal MRI characterizes the impact of prenatal irradiation on ageing

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Synopsis

Prenatal exposure to ionising radiation can severely compromise brain development, leading to functional impairment of the brain. Behavioral deficits and/or morphological alterations have been reported, but the consequences of prenatal irradiation at older age remains unexplored. We irradiated pregnant mice with different doses ((0.05 to 1.0Gy)) at embryonic day 11 and investigated structural sequellae at an old age using in vivo longitudinal MRI. Apart from small brain size, we noticed predominant regional changes and increase in brain volume as the mice aged ((unlike humans)). Hippocampus seems to be affected by exposure to even low-doses and relates to impaired spatio-cognitive performance.

Introduction

In utero radiation exposure resulted in an increased prevalence of neurological aberrations, including mental disability and decreased IQ levels, in the atomic bomb survivors of Hiroshima and Nagasaki(1,2). While the interaction between radiation exposure and ageing processes has been reported(3,4), investigating the consequences of prenatal irradiation at older age is unexplored. Apart from these epidemiological studies, investigating the in-vitro and in-vivo animal models to further explore such a relationship is interesting. Previous animal experiments have evidenced that radiation exposure of the young adult brain can result in an early molecular response associated with cognitive dysfunction, advanced ageing and Alzheimer disease(5). Also, excessive DNA damage during brain development was found to drastically accelerate ageing(6), indicating that gestational distress might have profound effects for the onset of ageing processes in postnatal/adult life(7). This has never been investigated in the light of prenatal exposure to radiation. Here, we explore for the first time whether in utero radiation exposure might affect brain ageing. To this end, we irradiated pregnant mice with different doses (0.05,0.10,0.5 or 1.00 Gy) at embryonic day (E)11 and investigated structural sequelae at an old age using in vivo MRI.

Methods

At E11, pregnant C57Bl/6J mice were irradiated with different doses of X-rays (0.05, 0.10 and 1.0 Gy, N=50) using a Pantak HF420 RX instrument operating at 250 kV, 15 mA, 1 mm Cu-filtered X-rays (dose rate of 0.375 Gy/min). Animals (female offsprings) were imaged at the age of around 10, 30 and 90 weeks(w) after birth with a 9.4 Tesla Bruker Biospec Scanner (Bruker Biospin, Ettlingen, Germany with following parameters: 3D RARE,TR=1.3ms,TE=14.2ms, matrix 192×256×128,80µm resolution (isotropic). In addition, we subjected aged mice (90w) to 3D diffusion tensor MRI (DTI) imaging using single shot EPI with TR=1ms,TE=0.32ms,matrix128×96×64,156µm in-plane, 30 non-collinear directions with b-value 1500smm^{-2}. For morphological characterization of regional volumetric changes, T_2 images were first corrected for intra- and inter-scan intensity variations and a study-specific mean deformation template(8,9) was constructed by iterative non-rigid registration(10,11). By co-registering this template to a mouse brain atlas(12), the atlas labels(~19 structures) were propagated to the individual study images (**Fig 1**). Volume of brain structures (mean±SEM) were compared among different experimental groups by one-way ANOVA, with correction for post-hoc comparison (significance 0.05). Parametric maps of mean-radial-axial- diffusivity and fractional anisotropy from DTI data, were examined for dose-dependent differences at 90w.

Results

At all time points, the whole brain volume of animals exposed to 1.00Gy were smaller compared to controls and other low dose conditions (see **Fig 2**). Likewise, the absolute volumes of most of the brain regions (~16/19) of 1.00-Gy-irradiated mice were significantly small at all three time points. Although the whole brain volume increased over time in all groups, only the increase in the control group between 10w and 30w was significant. While most brain regions like ventricles, showed increase in volume over time, structures like posterior/frontal cortex and striatum, did not change. Interestingly, the midbrain was significantly reduced in a dose-dependent manner for the 0.05-, 0.10- and the 1.00-Gy-exposed mice at 10w and 30w, but not at 90w. Also, the hippocampus was the only structure that was significantly reduced in volume in all irradiated conditions at 90w (**Fig 3,4**). Unlike the previous reports on enlarged ventricles or hydrocephaly following in utero radiation(13), ventricle volumes did not show any significant increase in a dose dependent manner. Our preliminary analysis of the DTI data at 90w included only hippocampus region, which did not show differences in parametric maps.

Discussion & Conclusion

We followed-up the alterations in brain morphology induced by prenatal irradiation over time using in vivo 3D T2-weighted MRI. The high-dose exposed animals clearly exhibited microcephaly, thereby leading to decrease in absolute volumes. Animals exposed to low-dose condition also demonstrated alterations in regional volumes like mid-brain and hippocampus, which are brain structures known to be particularly affected by ageing. Absence of hydrocephalus condition could not be explained, although experimental conditions remained identical to(13). Further, the longitudinal MRI allowed us to visualize the growth of the mouse brain over time, which matches with literature(14). In contrast, the human brain volume declines with age and in particular, hippocampal atrophy is closely linked to dementia and ageing-dependent cognitive decline. Of interest, this link between hippocampal structure and function might be of relevance for our finding of a decreased hippocampal volume in aged prenatally irradiated mice. This might attribute to the impaired spatio-cognitive performance that was assessed in a behavioral test battery previously reported on the same animals. Ongoing work on DTI analysis for the whole brain, may provide insight on white matter differences.

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Figures

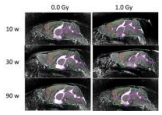

Fig 1: Longitudinal MRI of mouse brain from control (0.0 Gy) and irradiated (1.0 Gy) groups. The anatomical labels propagated from a mouse brain atlas (cyan-brain, pink-ventricles, red-frontal cortex, green-posterior cerebral cortex) are overlaid on the native space intensity images.

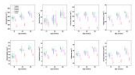

Fig 2: Whole brain volume and regional structures predominantly increase in volume over time. The effect of irradiation is most evident in the 1.0Gy condition, which shows small brain volume at 10, 30 and 90-weeks.

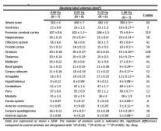

Fig 3: Absolute volume of brain structures from 90 week old prenatally irradiated mice, as computed from atlas-based label propagation. Animals from 1.0Gy condition, show a strong reduction in global and regional brain volumes. Measures from 0.50 Gy at 90w were excluded from statistical analysis due to very small sample size.

Fig 4: The volumes measures normalized to the mean control volumes of each structure at 90w time point. Hippocampus is distinctly lower compared to the control volume for all the four irradiation conditions, likely indicating the impact of even low doses on ageing.